BLOOD PRODUCTS ADVISORY COMMITTEE

Pooled Plasma (Human), Solvent/Detergent Treated (Octaplas™)

BLA 125416/0

For BPAC Meeting: September 20, 2012

octapharma

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EXECUTIVE SUMMARY

The briefing package summarizes the Biological License Application (BLA) for Pooled Plasma (Human), Solvent/Detergent (S/D) Treated.

octaplasLG® is indicated for:

- management of preoperative or bleeding patients who require replacement of multiple plasma coagulation factors;
- substitution of intentionally removed plasma (e.g. plasma exchange in patients with thrombotic thrombocytopenic purpura (TTP)).

octaplas® was developed as an alternative to single-donor fresh-frozen plasma (FFP) in order to increase the safety of plasma transfusion by minimizing the risk of viral transmission. octaplas® is prepared from 630 to 1520 single-donor units of the same blood group (batch size 380 liters). During the manufacturing process, whole cells and cell fragments/debris are removed by 1.0 µm size-exclusion filtration. Subsequently, the plasma pool is treated with a combination of the solvent [1% Tri(n-butyl)phosphate (TNBP)] and detergent (1% Octoxynol-9) to inactivate any enveloped viruses. These S/D reagents are later removed by oil and solid phase extraction, respectively. After 0.2 µm sterile filtration, octaplas® is filled into 200 mL bags and rapidly deep-frozen.

S/D treatment has become the gold standard method used for the effective and robust inactivation of all enveloped pathogens. The S/D reagents utilized irreversibly disrupt the lipid membrane of the virus rapidly and completely through a non-selective mode of action. The efficacy of the S/D method to inactivate enveloped viruses rapidly, irreversibly and completely has been clearly demonstrated for octaplas® by extensive pre-clinical virus validation studies, clinical safety virology assessments and by the long-term post-marketing clinical experience. The pooling of approximately 1000 plasma donations levels out the single-donor specific variability in terms of key coagulation proteins and other important plasma constituents such as immune neutralizing antibodies. Combined with a routine comprehensive nucleic acid amplification test (NAT) screening program, the presence of standardized levels of neutralizing antibodies in the plasma pool and final container minimizes the risk of transfusion-relevant non-enveloped viruses such as hepatitis A virus (HAV), hepatitis E virus (HEV) and parvovirus B19. Furthermore, the pooling also results in a significant dilution and neutralization of anti-granulocyte (HNA) and anti-human lymphocyte antigen (HLA) antibodies, thereby abolishing the risk of severe adverse events like transfusion-related acute lung injury (TRALI). The therapeutic safety and efficacy of octaplas® has been demonstrated through the treatment of more than 2.6 million patients using over 7.8 million bags since 1992.

The evaluation of the octaplas® manufacturing process to remove potentially present pathologic prion proteins (PrP^{Sc}) revealed an overall capacity of 2.5 $\log_{10}$.[1] A further extension of this removal capacity has been evaluated and a new chromatographic step for the selective binding of PrP^{Sc} to an affinity ligand, developed and optimised for PrP^{Sc} capture (≥9.06 $\log_{10}$ ID/3.8 liters production gel, respectively ≥5.64 $\log_{10}$ ID_{50}/mL gel) and being attached to synthetic resin particles, was implemented into the manufacturing process of octaplasLG®. In addition to the introduction of this novel prion removal technology, the time of S/D treatment was reduced from 4–4.5 to 1–1.5 hours, in order not to prolong the overall process time and to possibly improve those plasma proteins that may suffer from long S/D treatment and/or long manufacturing time. The virus validation studies and long-term clinical experience with the very robust S/D treatment used for

octaplas® justify this shortening. The new product was called octaplasLG® (LG, ligand gel).

octaplasLG® is a solution for infusion and it is classified in the following pharmaco-therapeutic group: Plasma substitutes and plasma protein fractions, ATC code: B05AX03.

The active ingredient (human plasma proteins) consists of all the normal components of plasma such as albumin, immunoglobulins and other globulins, coagulation factors and complement factors, and their inhibitors. The total protein concentration is 45–70 mg/mL and the protein distribution is within the normal range for human plasma. The coagulation activity values are close to the corresponding values for normal human plasma and a minimum of 0.5 IU/mL.

octaplasLG® is manufactured at Octapharma's factories in Vienna, Austria and Stockholm, Sweden.

Please note that you will find in the enclosed documentation the following different trade names and products due to respective product development phases:

octaplas®: blood group specific, S/D treated (4–4.5 hours) virus-inactivated pooled plasma (without the specific prion removal column); the product was first approved in Germany in 1989; today it is approved in 19 authorities worldwide.

octaplasLG®: blood group specific, S/D treated (1–1.5 hours) virus-inactivated pooled plasma including prion removal technology. The abbreviation "LG" was added to the product name during development of prion removal technology. Today octaplasLG® is approved in Australia, United Kingdom, Belgium, Finland, Ireland, Luxembourg, The Netherlands, Sweden, Portugal, Switzerland and Germany. Variations to change other existing octaplas® licenses to octaplasLG® are currently ongoing.

Product to be licensed in USA as Octaplas™.

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1.0 INTRODUCTION

octaplas® was specifically developed as an alternative to fresh-frozen plasma (FFP) in order to prevent virus transmission and to provide a product with standardised amounts of active ingredients.

octaplasLG® is a solvent/detergent (S/D) treated frozen human plasma prepared from units of FFP pooled according to their specific blood groups A, B, O, or AB. Thereby, the coagulation factor and inhibitor activities in the final product become more standardized, resulting in a higher therapeutic reliability compared to standard FFP. octaplasLG® contains the normal constituents of human blood plasma.

octaplasLG® is presented as a solution for infusion, containing 9–14 g human plasma proteins per plasma bag (200 mL), which equals 45–70 mg/mL. The product is supplied as a frozen solution.

octaplasLG® is indicated for:

- the management of preoperative or bleeding patients who require replacement of multiple plasma coagulation factors.
- the substitution of intentionally removed plasma (e.g. plasma exchange in patients with thrombotic thrombocytopenic purpura (TTP)).

2.0 PRODUCT DESCRIPTION AND CHARACTERLZATION

2.1 Product Composition

Table 1 Composition

Name of Active Ingredients	Quantity per 200 mL Bag	Function	Standard
Human plasma proteins	9.0 – 14.0 g	Active ingredient	internal

Name of Excipients	Quantity per 200 mL Bag	Function	Standard
Sodium citrate dihydrate	0.88 – 1.48 g	Anticoagulant	Ph.Eur., USP
Sodium dihydrogen-phosphate dihydrate	0.06 – 0.24 g	Buffer component	Ph.Eur., USP/NF
Glycine	0.80 – 1.20 g	Osmolality regulator	Ph.Eur., USP/NF

The active ingredient (human plasma proteins) consists of all the normal components of plasma such as albumin, immunoglobulins and other globulins, coagulation factors and complement factors, and their inhibitors. The total protein concentration is 45–70 mg/mL and the protein distribution is within the normal range for human plasma. The coagulation activity values are close to the corresponding values for normal human plasma and a minimum of 0.5 IU/mL for each coagulation factor is specified. However, plasma lipids and lipoproteins are reduced due to the virus inactivating S/D treatment and the subsequent oil extraction and solid phase extraction.

No antimicrobial substance or preservative is added.

Sodium citrate is not added during the production process; it is present in the source plasma as an anticoagulant.

2.2 Proposed Indication and Proposed US Trade Name

octaplasLG® is indicated for:

- Management of preoperative or bleeding patients who require replacement of multiple plasma coagulation factors.
- Substitution of intentionally removed plasma (e.g. plasma exchange in patients with thrombotic thrombocytopenic purpura – TTP).

The proposed trade name for octaplasLG® in US is Octaplas™.

2.3 Dosing

Dosage in management of preoperative or bleeding patients

An adequate hemostatic effect in minor and moderate bleedings or surgery is usually achieved after the infusion of 5–20 mL octaplasLG®/kg BW. This should increase the patient's plasma coagulation factor levels by approximately 10% to 33%. In the event of major hemorrhage or surgery, higher doses become necessary. It is important to monitor the response, both clinically and with measurement of e.g. activated partial thromboplastin time (aPTT), prothrombin time (PT), and/or specific coagulation factor assays.

Dosage in substitution of intentionally removed plasma (plasma exchange)

The plasma volume removed during plasmapheresis should be replaced (exchanged) with octaplasLG® completely.

2.4 Manufacturing and Virus / Prion Safety

octaplasLG® is manufactured out of "PLASMA“ acc. 21 CFR 640.30 and "SOURCE PLASMA" acc. 21 CFR 640.60.

To reduce the risk of transmission of infective agents, stringent controls are applied to the selection and screening of donors for hepatitis B, hepatitis C and HIV infection. The plasma pools are also tested for HBsAg, anti-HIV 1/2, HBV-NAT, HIV-NAT, HCV-NAT, HAV-NAT, HEV-NAT and parvovirus B19-NAT and only those found negative or below a given cut-off limit (parvovirus B19, ≤10 IU/µL) are used for manufacturing.

S/D treatment is not effective against non-enveloped viruses, including parvovirus B19, HEV and HAV. However, the presence of standardized levels of neutralizing antibodies in the plasma pool and final container minimises, in addition to the virus load control by NAT screening, the risk of transmitting non-enveloped viruses such as HAV, HEV and parvovirus B19.

An overview on the manufacturing steps of octaplasLG® is given in Table 2.

Table 2 Manufacturing Steps for octaplasLG®

Fast thawing and pooling of single FFP units
Removal of cells, fragments and aggregates by 1.0 µm filtration
S/D treatment (1% TNBP & 1% Octoxynol for 1-1.5 hrs at +30°C ± 1°C)
Castor oil extraction of TNBP, clear filtration and solid phase extraction of Octoxynol
Addition of glycine
Affinity chromatography for PrP^{sc} capture
Sterile filtration (0.45 µm and 0.2 µm)
Aseptic filling, sealing of bags and fast freezing (≤ -60°C) and storage (≤ -30°C)
Full quality control and release of final product

The validation studies were performed by Octapharma PPGmbH's Virus & Prion Validation Department, Frankfurt/Main, Germany. All studies were performed with representative intermediate process material collected from routine production prior to the process step to be validated.

The Overall Summary in Table 3 gives an overview about the global reduction factors during manufacture of octaplasLG®.

Table 3 Global Reduction Factors During octaplasLG® Manufacturing

Step	HIV-1	PRV	SBV	BVDV	WNV	VACV
Immune neutralization [log_{10}]	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
S/D treatment [log_{10}]	≥ 6.18	≥ 5.03	≥ 5.31	≥ 5.12	≥ 5.63	≥ 5.00
Global reduction factor [log_{10}]	**≥ 6.18**	**≥ 5.03**	**≥ 5.31**	**≥ 5.12**	**≥ 5.63**	**≥ 5.00**

Step	HSV-1	HAV	COX-B6	POL-1
Immune neutralization [log_{10}]	≥ 11.1 (pool)	≥ 10.0 (pool)	≥ 8.6 (pool)	≥ 10.9 (pool)
S/D treatment [log_{10}]	Not applicable	Not applicable	Not applicable	Not applicable
Global reduction factor [log10]	**≥ 11.1 (pool)**	**≥ 10.0 (pool)**	**≥ 8.6 (pool)**	**≥ 10.9 (pool)**

The capacity to remove prions has been assessed in a two-step approach for the process in accordance with the "Guideline on the investigation of manufacturing processes for plasma-derived medicinal products with regard to vCJD risk" (CPMP/BWP/5136/03).

3.0 DEVELOPMENT OVERVIEW

3.1 Developmental Approach

octaplas® was developed and introduced by Octapharma in the early 1990s. Today, octaplas® is the World's most widely used, S/D treated plasma, and the product has obtained marketing authorization in many European countries. octaplas® was developed as an alternative to FFP with the following objectives:

- To reduce the risk of virus transmission.
- To meet the request for a standardised, cell free and high quality coagulation–active plasma for infusion such that therapeutic accuracy is improved and treatment–related adverse events (AEs) are reduced, such as transfusion-related acute lung injury (TRALI).
- To prevent sepsis resulting from transient bacteremia of donors or accidental bacterial contamination during collection of blood.
- To increase the prion safety via introduction of a prion removal step.

3.2 Regulatory History

octaplas® was first approved in Germany in November 1989.

Today, octaplas® is approved in 19 countries and in addition, octaplasLG® is approved in 11 countries worldwide.

For Finland, octaplasLG® is also produced in the framework of a self-sufficiency program. This involves receiving plasma from the country, manufacturing at Octapharma's production plants, and returning the finished product to the country of origin for distribution.

3.3 Overview of Preclinical Studies

Since octaplasLG® is a blood group specific plasma which contains 45–70 mg/mL of human plasma proteins, standard pharmacodynamic and toxicity studies generally carried out for new substances in commonly used species are not applicable to this product.

octaplasLG® contains the following excipients: sodium citrate dihydrate, sodium dihydrogenphosphate dihydrate, and glycine.

The excipients used are very common in pharmaceutical formulations. The specifications in the formulation strictly follow the specifications of the European Pharmacopoeia. Taking into account the amount of the excipients in the final formulation, no toxicity is expected following the intended therapeutic use of octaplasLG®. However, high infusion rates may cause effects because of citrate toxicity (fall in ionised calcium); especially in patients with liver function disorders.

A combination of TNBP (tri-n-butyl phosphate) and Octoxynol-9 (TRITON X-100) is used in an S/D process to inactivate viruses during the manufacturing of octaplasLG®. The product is mixed with 1% TNBP and 1% Octoxynol-9. Subsequent castor oil extraction and solid phase (C-18) extraction serve to eliminate the S/D reagents, leaving residual amounts of TNBP and Octoxynol-9 of maximally 2 ppm (<2 µg/mL) and 5 ppm (<5 µg/mL), respectively.

The use of TNBP and Octoxynol-9 in humans has a long history: In 1991, Horowitz [2] stated that Factor VIII concentrates prepared with TNBP (and a detergent) were licensed by the Food and Drug Administration in 1985. As a consequence, many patients with hemophilia must have received TNBP treated products exclusively or principally for 6 years. At that time, on a worldwide basis, approximately 2×10^9 IU of coagulation factor concentrates had been infused, equivalent to 20,000 man-years at 100,000 units per man-year. Further focusing on TNBP, Horowitz calculated that occupational exposure (8 hours, 5 mg per m^3) would represent a daily intake of about 10 mg, "well above that encountered on infusion of TNBP treated products".

Octoxynol was used by women as a spermicide over many years with doses of 50–130 mg being used per application [3] and turned out to be well tolerated. The literature focuses on reproduction outcome after application of Octoxynol to humans as a spermicide.

In summary, animal and in vitro experiments and the experience gained in patients suggest the safe use of TNBP and Octoxynol-9 in octaplasLG®. No toxic reactions have to be expected.

Genotoxicity and carcinogenicity have not to be considered for TNBP and Octoxynol-9 and there are no adverse effects on reproduction.

4.0 CLINICAL DEVELOPMENT PROGRAM

The clinical development of octaplas® started in the early 1990s. Both prospective clinical trials and retrospective surveys have been performed since then. About one half of the

trials were Octapharma-sponsored, the other half were investigator-initiated/sponsored. In addition to these studies, individual case reports were published.

In total, 15 prospective clinical studies and 9 retrospective studies with octaplas®/ octaplasLG® have been conducted.

In total, about 495 patients have been enrolled in the pro- and retrospective *efficacy* studies, including one observational study (see Table 4), and the patients were exposed to 2592 infusion episodes with octaplas®/octaplasLG®. Even though the efficacy studies were quite heterogeneous, the main indications can be grouped as shown in Table 4:

Table 4 Pro- and Retrospective Efficacy Studies with octaplas®/octaplasLG® – Overview of Main Indications

Indication	Reference	Number of Patients Studied*
Inherited or acquired single or combined coagulation factor deficiencies	[4] [5]	11 17
Heart/thoracic surgery	[6] [7] [8]	20 36 55
Liver disease (LD) or liver surgery including liver transplantation (LTX)	[9,10]	27
Coagulopathy (not elsewhere classified)	[11] [12]	30 111
Reversal of oral anticoagulants in cardiopulmonary bypass surgery	[13]	20
Plasma exchange (PEX) in TTP patients	[14] [15] [16]	3 32† 8
PEX procedures Peri-/intraoperative use Consumptive coagulopathy/ DIC Non-surgical bleeding Other	[17]	32 43 30 11 9
	TOTAL	**495**

* Only patients on S/D treated plasma counted; † Exact figure not given.

5.0 SUMMARY OF EFFICACY

Single-donor FFP contains physiological levels of functionally active plasma proteins according to their respective intra individual variations.

S/D treated plasma is produced from plasma pools consisting of 630 to 1520 single donor units (batch size 380 liters). Thereby, the coagulation factor and inhibitor activities in the final product become more standardized which results in a higher reliability compared to standard FFP. On the other hand, as a consequence of the S/D manufacturing process, S/D treated plasma contains lower activities of plasmin inhibitor and protein S.[18] In an attempt to further optimize the manufacturing process of Octapharma's S/D treated plasmas, the S/D treatment time was reduced. This resulted in higher plasmin inhibitor activities which will be advantageous from an efficacy point of view.

Overall, octaplasLG® provides an acceptable balance between improved viral and prion safety, the desired standardization and the partly impaired plasma activity.[19]

In addition to the studies included in the BLA, evidence is also based on expert opinions, expert group consensus guidelines, and case reports.

A total of 9 clinical practice guidelines addressing the use of plasma have been identified in the literature and reviewed.[20-28] Of these, 3 are dedicated to the use of plasma in specific clinical settings: coronary artery bypass grafting [24], obstetrics [20] and peri-operative and obstetric use [21]. The remaining guidelines provided general indications for use, particularly the appropriate clinical settings. All guidelines were developed and endorsed by major medical societies or organizations.

Only a few clinical trials have evaluated the use of standard FFP in patients [29-32], and most recommendations are based on clinical observations and the results of coagulation tests.

In contrast, S/D treated plasma has been assessed in several clinical trials and a brief overview is provided in Table 5. Most of the studies listed in this table were actually done with octaplas®/octaplasLG®, the remaining 2 were investigating the US product [33] or a product manufactured by the German Red Cross [34].

Table 5 Prospective Clinical Trials on the Efficacy of S/D Treated Plasma

Study Group	Study Design; No. of Subjects	Clinical Setting	Main Results
Hellstern et al. [11]	prospective; *octaplas* n = 30	coagulopathy	significant decrease in PT, significant increase in fibrinogen and antithrombin levels
Solheim et al. [6]	prospective; *octaplas* n=20, FFP n=20, "no plasma" n=26	open heart surgery	no clinical difference
Williamson et al. [9,10,14]	prospective, randomized; n=55; *octaplas* vs. FFP	coagulopathy in LD or LTX; TTP	equal correction of coagulation parameters, equal clinical efficacy
Haubelt et al. [8]	prospective; *octaplas* n=36, vs. FFP n=31	open heart surgery	no clinical difference, significant differences in pre- and post-treatment protein S and plasmin inhibitor activities
Solheim et al. [6]	prospective; *octaplas* n=19 vs. *Uniplas* n=36 vs. "no plasma" n=29"	open heart surgery	no clinical difference between the 2 active treatments
Santagostino et al. [5]	prospective; *octaplas* n=17	congenital deficiencies	fully effective in 81% of cases
Inbal et al. [7]	prospective; *octaplas* n=11	hereditary or acquired isolated or combined coagulation factor deficiency	bleedings stopped, no abnormal bleeds observed; overall good efficacy
Multicenter [17]	prospective, observational, *octaplas* n=65; *octaplasLG* n=60	scheduled for urgent or semi-urgent cardiac surgery	treatment success was 100% after both, *octaplas* or *octaplasLG* for any indication investigated,

			except for PEX (92.3% and 89.5% for the two treatments, respectively)
Demeyere et al. [13]	prospective, randomized; *octaplas* n=20 vs. PCC n=20	reversal of oral anti-coagulants in urgent or semi-urgent cardiac surgery	PCC reverses anticoagulation safely, faster and with less bleeding than S/D treated plasma
Lerner et al [33]	prospective, randomized; S/D treated plasma n=22 vs. FFP n=23	coagulopathy	no clinical differences, no difference in correction of PT
Beck et al [34]	prospective; S/D treated plasma n=17 vs. FFP n=23	coagulopathy	no differences in coagulation parameters, no clinical difference

Difference between FFP and S/D Treated Plasma

Despite some differences in the composition of FFP and S/D treated plasma, prospective controlled and observational studies have failed to reveal any significant difference in clinical efficacy or tolerance between the 2 types of plasma. If properly produced, FFP and S/D treated plasma are virtually free of activated coagulation factors and can be used safely even in patients with an activated hemostasis.[18] Therefore, with respect to efficacy, FFP and octaplas®/octaplasLG® can be considered to be essentially equal.

In terms of safety, S/D treated plasma has some advantages compared to standard FFP.

As a consequence of the S/D manufacturing process, octaplas® contains lower activities of plasmin inhibitor and protein S, which are reduced by 75% and 40%, respectively. The activities of other coagulation factors and inhibitors are about 0% to 30% lower than in the plasma pools.[18] The reduced content of plasmin inhibitor in S/D treated plasma versus its content in single-donor FFP is well known from several previous publications.[8,35-38] It is worth noting that octaplas® contains normal, standardized levels of plasminogen.

The introduction of the ligand gel chromatography in the manufacturing process of octaplasLG® improved the prion safety. Furthermore, shortened S/D treatment for the "LG" plasmas has increased values for plasmin inhibitor and slightly increased values for protein S which are reduced by about 30% to 35% only, compared with FFP.

Hyperfibrinolysis:

In 2002, de Jonge et al. reported a significantly increased incidence of hyperfibrinolysis (75% versus 29%) in the patients (total n=41) undergoing LTX that received octaplas® compared to the patients that received single donor FFP.[39]

The findings from de Jonge were not in line with the Norwegian experience: since octaplas® replaced FFP in Norway in 1993, there have been no reports of increased fibrinolytic tendency in liver transplants. However, recognizing that plasmin inhibitor is a serine protease inhibitor that is synthesized in the liver, the infusion of S/D treated plasma in combination with the serine protease inhibitor "aprotinin" may have ensured a more favorable outcome than reported by the Dutch investigators.[40] Thus it appears that a proper way to prevent or reduce hyperfibrinolysis-induced bleeding in liver transplants is the timely administration of an antifibrinolytic agent rather than plasma transfusion.[40,41] Sarode et al. stated that patients undergoing LTX who experience heightened fibrinolysis when given S/D treated plasma will receive adequate pro-coagulant factors that correct the standard, commonly performed coagulation tests.[42] However, because of the deficiency

of plasmin inhibitor and the normal amount of plasminogen in S/D treated plasma, there will be ongoing conversion of plasminogen to plasmin by excessive endothelial-derived tissue plasmin activator. With this reduced neutralization of plasmin by plasmin inhibitor, there will be a further increase of fibrinolysis, which will lead to an increased tendency to bleed. Williamson LM replied to this letter based on a revisit of the raw data and the search for information from LTX centers that use only S/D treated plasma in LTX patients.[43] It was stated that hyperfibrinolytic problems were not investigated and not mentioned in the article due to the standard prophylactic use of antifibrinolytic drugs in the participating centers in the UK. The study did not have the statistical power to give firm evidence as to whether patients given octaplas® required greater blood component support.

Furthermore, a Letter to the Editor by de Jonge warrants special attention.[44] In this letter, the statements made by the author in his original article were somehow given a different slant. During the study period, the authors experienced serious hemostatic problems with substantial blood loss that – according to de Jonge – may partly be attributed to the limited number of transplantations performed at his centre and to the use of an LTX technique without piggyback anastomosis. In patients with normal pre-operative coagulation tests and little blood loss, no cases of hyperfibrinolysis were seen following octaplas® transfusion. Even more importantly, after the introduction of a piggy back anastomosis technique, blood loss decreased considerably at their centre. In addition, a low dose aprotinin treatment scheme was introduced in addition to octaplas® and since then 120 patients have undergone an LTX without any thrombotic complications.

In summary, we agree that hyperfibrinolysis cannot be corrected by using S/D treated plasma when plasmin inhibitor is the reason for the hyperfibrinolysis, due to a further dilution of the plasmin inhibitor. In this clinical setting, antifibrinolytic drugs should be used. The FFP patients received treatment for their fibrinolysis with antifibrinolytic drugs rather than single-donor FFP. The authors recommend *routine* administration of antifibrinolytic drugs when using S/D treated plasma. An appropriate warning is included in the proposed octaplasLG® label.

However, the time of S/D treatment in the manufacturing process of octaplasLG® has been shortened from 4–4.5 hours to 1–1.5 hours as compared with the original process. This measure improves (increases) the values for plasmin inhibitor and slightly increased the values for protein S without affecting the virus safety of the product.

Recommendations for Use

According to the guidelines of the American Association of Blood Banks (AABB) (see Table 6) the following indications for use of plasma (i.e. FFP and S/D treated) can be regarded as generally accepted:

- Management of preoperative or bleeding patients who require replacement of multiple plasma coagulation factors (e.g. liver disease)
- Patients with massive transfusion who have clinically significant coagulation deficiencies
- Patients on warfarin who are bleeding or need to undergo an invasive procedure before vitamin K could reverse the warfarin effect or who need to have anticoagulation therapy after the procedure
- For transfusion or plasma exchange in patients with thrombotic thrombocytopenic purpura (TTP)
- Management of patients with selected coagulation factor deficiencies, congenital or acquired, for which no specific coagulation concentrates are available

For octaplasLG®, the following indications are claimed:

- Management of preoperative or bleeding patients who require replacement of multiple plasma coagulation factors
- Substitution of intentionally removed plasma (e.g. plasma exchange in patients with thrombotic thrombocytopenic purpura – TTP)

A comparison between the indications claimed for octaplasLG® and published treatment guidelines is provided in the following table (Table 6).

Table 6 Comparison of Proposed Indications for Use of *octaplasLG* versus International Guidelines

Proposed *octaplasLG* Patient Information Leaflet	**American Guidelines [27]**	**Australian Guidelines [26]**	**Canadian Guidelines [22]**	**British Guidelines [28]**
Management of preoperative or bleeding patients who require replacement of multiple plasma coagulation factors	Management of preoperative or bleeding patients who require replacement of multiple plasma coagulation factors (e.g., liver disease). Massive transfusion that have clinically significant coagulation deficiencies.	Treatment of multiple coagulation deficiencies associated with acute DIC. In the presence of bleeding and abnormal coagulation parameters following massive transfusion or cardiac bypass surgery or in liver disease.	Patients with acute DIC with active bleeding associated with increased PT, INR or APTT, provided that the triggering condition can also be treated effectively.	In the presence of bleeding and abnormal coagulation, FFP may be indicated for massive transfusion; liver disease; and cardiac bypass surgery.
Substitution of intentionally removed plasma (e.g. plasma exchange in patients with thrombotic thrombocytopenic purpura - TTP).	For transfusion or PEX in patients with TTP.	Treatment for TTP often in conjunction with PEX.	Treatment of TTP followed by daily plasmapheresis with either cryosupernatant plasma or plasma as replacement fluid.	Treatment of TTP often in conjunction with PEX.

The dosing recommendations for FFP and S/D treated are mainly based on expert opinions, case reports, and on controlled and uncontrolled observational studies.

When compared with coagulation factor concentrates, plasma contains low concentrations of coagulation factor and inhibitor activities. Assuming an average coagulation factor and inhibitor potency of 1 IU/mL, 1 mL plasma/kg of body weight can increase coagulation factor and inhibitor levels by 1–1.5 IU/100 mL if the patient is at steady state. Increased turnover of coagulation factors and inhibitors due to blood loss and/or consumption reduces the in vivo recovery to 0.5–1.0 IU/100 mL or even lower. Hence, the rapid infusion of at least 10 mL plasma/kg BW is required to significantly increase the respective plasma protein levels. This in turn carries the risk of volume overload.[18]

The following dose recommendation can be given:

- For dosing in the management of preoperative or bleeding patients, an adequate hemostatic effect in minor and moderate bleedings or surgery is usually achieved after the infusion of 5–20 mL octaplasLG®/kg BW. This should increase the patient's plasma coagulation factor levels by approximately 10% to 33%. In the event of major hemorrhage or surgery, higher doses become necessary. It is important to monitor the response, both clinically and with measurement of e.g. activated partial thromboplastin time (APTT), prothrombin time (PT), and/or specific coagulation factor assays.
- For dosing in substitution of intentionally removed plasma, the plasma volume removed during plasmapheresis should be replaced (exchanged) with octaplasLG® completely.

6.0 SUMMARY OF SAFETY

In terms of safety, S/D treated plasma has some advantages compared to standard FFP:

- It has a reduced risk of virus transmission.
- It is more standardized which results in a higher therapeutic reliability.
- There is a reduced incidence of TRALI due to the dilution of potential high-titer HNA and/or HLA antibody–containing donations.
- There is a reduced incidence of hypersensitivity type reactions due to the removal of cells and cell debris during the manufacturing process.
- It is a pharmaceutical product, manufactured under GMP conditions, thereby preventing sepsis resulting from transient bacteremia of donors or accidental bacterial contamination during collection of blood/plasma.

Additionally, manufacturing of the "LG" plasma products (octaplasLG®) was developed to increase the prion safety and improve the product characteristics, i.e. to increase the plasmin inhibitor and to a smaller degree the protein S levels.

Nowadays, allergic/anaphylactic reactions and TRALI are the dominating AEs linked to plasma transfusion. The risk of viral transmission has been reduced significantly by introducing virus inactivation techniques and/or NAT techniques. Although no cases of variant Creutzfeldt-Jakob transmission to humans by blood plasma have been reported until now, Octapharma has introduced a prion reduction step (ligand column chromatography) in the manufacturing process of octaplasLG®.

TRALI has nearly as high an incidence of mortality and major morbidity as that reported for the transfusion of incorrect blood components. The specific mechanisms remain unclear, but a major contribution may be related to the presence of alloantibodies. In an in-vitro study, Sinnott et al. investigated 58 single donor FFP bags and 12 samples of

octaplas® and tested them for the presence of HLA antibodies.[45] All octaplas® samples were found negative. In contrast, 5 FFP samples (9%) tested positive. This may explain why – in contrast to standard FFP – no TRALI cases have been observed with octaplas®/octaplasLG® to date.

Based on all the biochemical features of S/D treated, the risk for treatment–related AEs has in reality been reduced to only a limited amount of moderate to severe allergic/anaphylactic type of reactions. In addition, by eliminating the TRALI problem, especially the immediate death caused by TRALI, S/D treated has contributed to solving a major problem in transfusion medicine.

The following treatment–related AEs have been observed for octaplas®/octaplasLG® (or S/D treated plasma):

- Acute mild and sometimes severe allergic reactions characterized by urticaria, fever, chills, nausea, vomiting, hypotension, chest pain, bronchospasms, and dyspnea.
- High infusion rates may cause cardiovascular effects as a result of citrate toxicity (fall in ionized calcium), especially in patients with impaired liver function. In the course of plasma exchange procedures, symptoms attributable to citrate toxicity such as fatigue, paresthesia, and tremor may be observed.
- The administration of octaplasLG® must be based on AB0-blood group compatibility. In case of an incompatible infusion, AB0-antibodies in octaplasLG® will bind to the antigens of the recipient's red blood cells and may cause minor hemolytic transfusion reactions.
- High dosages or infusion rates may induce hypervolemia with consecutive pulmonary edema and/or cardiac failure.

The overall incidence of treatment–related AEs associated with S/D treated seems to be lower than that observed with standard FFP, as evidenced in countries in which standard FFP and other plasma was replaced for transfusion by S/D treated plasma. In two retrospective comparative analyses, focusing on safety aspects, all patient groups including preterm infants and liver transplantation patients have been considered.

In Norway, octaplas® products (lyophilized, S/D treated, blood group specific; and liquid, S/D treated, blood group specific) have totally replaced standard FFP, since 1993.[46] From 1993 until 2003, no thrombotic or fibrinolytic complications have been observed when octaplas® was infused under routine clinical conditions to a variety of patients, nor any virus transmissions or cases of TRALI; the latter is a common side effect linked to transfusion. The only serious AE after treatment was due to the misuse of 4 units as acute volume replacements. The rapid infusion caused a fall in calcium (due to citrate) and a subsequent cardiac arrest in an elderly patient.[46]

Finland discontinued the clinical use of standard FFP in May 2007 and introduced octaplas® as only plasma available for transfusion since then. The rate of serious adverse reactions has decreased substantially and no TRALI reactions were observed until October 2008.[47]

In most clinical studies conducted with octaplas®, clinical tolerability was assessed by monitoring of vital signs, hematological (hemoglobin, hematocrit, full blood cell count) and other laboratory parameters. In addition, monitoring of AEs was performed according to applicable standards in force at the time. Viral markers were assessed with immunoassays or NAT techniques. Finally, an overall tolerability assessment was done in some studies by the treating physician and the patient using a non-validated verbal rating scale.

In prospective clinical studies, the rarer treatment–related AEs are usually not observed, because of the relatively small sample sizes. Therefore, the safety information obtained after marketing authorization becomes important because during this phase these rarer AEs are seen. Information is usually derived from post-authorization safety surveys and from the routine pharmacovigilance activities.

In the clinical studies, more than 2200 subjects received octaplas®/octaplasLG® manufactured by Octapharma. In the *prospective* studies (including one observational study, LAS-201), 369 patients received a total of 1575 infusion episodes with octaplas®/octaplasLG®. It is worth mentioning that one "infusion episode" (especially during PEX procedures in patients) could comprise administration of multiple units of octaplas®/octaplasLG®.

The average doses administered ranged from 5 to 38 mL/kg BW.

The incidence of serious treatment–related AEs was very low in the prospective clinical studies conducted with octaplas®: of the 337 patients who received octaplas® in these studies, only 1 had a serious treatment–related AE (0.3%), i.e. a cardiac arrest due to citrate toxicity.

Since the market introduction of octaplas® in the 90ies, about 7.8 million bags of octaplas®/octaplasLG® have been sold. Assuming a mean single dose of about 3 bags, this figure represents more than 2.6 million patient treatments with octaplas®/octaplasLG®.

During the post-marketing period, 130 out of 195 cases were classified as serious. It is important to note that this number includes *all* cases, irrespective of causality. In other words, cases with unlikely or no relationship to octaplas®/octaplasLG® treatment and cases which could not be classified in terms of causality due to limited or missing information are also included in this figure. A total of 82 serious cases were assessed as causally related to octaplas®/octaplasLG® treatment, as shown in Table 7.

Table 7 Overview on Serious Case Reports Observed During the Post-Marketing Period

Type of Report	Number of Unrelated Cases*		Number of Related Cases**	
	Octaplas	OctaplasLG	Octaplas	OctaplasLG
Suspected transmission of infectious agent	38	0	0	0
Hypersensitivity reactions including anaphylactic and allergic type of reactions	2	0	42	5
Seroconversions (passive transfer of antibodies)	0	0	5	0
Cardiac disorder (not elsewhere classified)	4	0	2	0
Circulatory overload	1	0	5	0
Respiratory disorder (not elsewhere classified)	2	0	10	2
Thromboembolism	0	0	4	0
Hyperfibrinolysis	0	0	1	0
Hemolytic transfusion reaction	0	0	0	0
TRALI	0	0	0	0
Citrate toxicity	0	0	1	0
Isolated fever and chills	0	0	2	0
Other (alkalosis, medication error, etc.)	2	0	2	1
TOTAL	**49**	**0**	**74**	**8**

* i.e. not related, unlikely, unclassifiable; ** i.e. possible or probable.

Thrombogenicity

Yarranton et al. have reviewed the occurrence of venous thromboembolism (VTE) in 68 consecutive patients with TTP.[48] In total, 8 VTE events were identified in 7 patients during PEX therapy. In 7 out of 8 events, octaplas® was the last plasma used prior to the VTE. octaplas® is known to have a slightly reduced protein S activity. Theoretically, this may contribute to an increased risk of VTE when large volumes are transfused.

It was acknowledged by the authors that VTE is a multi-causal disease and several known precipitating factors for VTE were undoubtedly present in all the reported cases. Venous thrombosis is a well-recognized complication of central venous catheter insertion, and an increased rate is seen in those who possess the Factor V Leiden mutation. Other known risk factors identified in the patients in this study were pregnancy, obesity, and family history.

In addition, all cases had complicated TTP that responded slowly to PEX alone and required adjuvant therapies. Furthermore, these patients usually had recovering platelet counts and under such conditions platelets are often more susceptible to activation. All these are possible further risk factors. It was also pointed out by the authors that octaplas® is potentially a very useful plasma in TTP patients. Like cryosupernatant (CSP), octaplas® lacks the largest von Willebrand factor multimers. This may be of theoretical benefit in

TTP, as the presence of the highest-molecular-weight multimers are thought to be implicated in the pathogenesis of TTP. A reduction in the number of allergic reactions is another potential advantage of octaplas®, given that the plasma pooling process results in extreme dilution of the antibodies that are responsible for an immune reaction. One patient in this study received octaplas® expressly for this reason. Additionally, patients with TTP have responded to octaplas® PEX after previous failure with FFP and CSP. It would, therefore, be inadvisable to prohibit the use of octaplas® in PEX for TTP treatment.

In conclusion, the significant morbidity and mortality associated with VTE makes prevention very important. This is especially relevant in patients with TTP because the requirement of therapeutic anticoagulation is likely to be complicated by low platelet counts. Therefore, we agree with the authors' recommendation that VTE prophylaxis should be used in all acute TTP patients. Fitted graduated elastic compression stockings (Class I) should be worn from the time of hospital admission, and prophylactic doses of low-molecular-weight heparin, in addition to low-dose aspirin, should be administered when the platelet count rises above $50x10^9$/L. Central venous catheters should be removed as soon as possible when no longer required. We also agree with the authors' recommendation that physicians need to monitor TTP patients for signs of VTE. However, this also applies to patients who receive CSP or standard FFP.

Immunogenicity

Since octaplasLG® does not contain red blood cells, leukocytes and platelets, the risk of immunization is reduced. Because octaplasLG® is free from antigen-bearing cell structures, it can be given to fertile women, irrespective of their Rhesus and Kell system factors. In contrast to octaplasLG®, the residual red blood cells in FFP may cause the development of anti-D and anti-K, which are able to cause hemolytic diseases in future children.

None of the safety data available from clinical studies suggest that inhibitor formation had occurred.

Viral Safety

In addition to donor selection and screening procedures used for the raw material and final product, octaplasLG® is virus inactivated by the S/D method. This method has been applied to many therapeutic products derived from human plasma and has established an impressive long-term and world-wide safety record. The S/D method provides reliable inactivation of enveloped viruses such as HIV-1, HBV, HCV, Vaccinia Virus (VACV), and West Nile Virus (WNV). This method irreversibly disrupts the envelope of such viruses and its associated binding sites rapidly and completely. This results in a complete inability for viruses to attach to and penetrate host cells, i.e. virus replication *in vivo*. The S/D inactivation addresses the limitations of donor selection and screening of donations such as denial of recent risk behaviors, sensitivity and specificity of tests, errors and quality assurance problems. The efficacy of the S/D method used in the octaplasLG® manufacturing process has been validated according to applicable guidelines in force at the time. These laboratory studies clearly demonstrate the reproducibility, the non-selective mode of action, and the robustness of this method which, taken together, contribute to the very high safety margin towards any enveloped viruses. When medicinal products prepared from human blood or plasma are given to a patient, the transmission of infectious agents cannot be totally excluded. This applies also to hitherto unknown pathogens. However, since the S/D method is of utmost efficacy when used to inactivate known enveloped viruses, the possibility of the transmission of even an unknown enveloped virus is remote.

From its mode of action it is clear that the S/D method has no significant inactivation or removal effect on non-enveloped viruses such as HAV, HEV and parvovirus B19. Thus, there is at least a theoretical possibility of an increased risk of transmitting these viruses by the pooling of plasma. However, the presence of neutralizing antibodies towards HAV, HEV and parvovirus B19 in the starting plasma and the final product results in immune neutralization and passive immunization which both serve to limit or prevent virus replication and thereby infection in patients.[49] Recipients of octaplasLG® at a dose of 10 mL/kg BW will receive approximately 100 mg polyvalent IgG/kg, ≥20 IU anti-HAV IgG, and ≥200 IU anti-B19 IgG/kg. This quantity actually exceeds what is for example recommended for HAV prophylaxis when administered as an intramuscular gammaglobulin preparation as pre– and post–exposure prophylaxis according to WHO guidelines. The principle of immune neutralization is well known and is probably the most important defense mechanism in preventing the infection of neighboring cells in patients with viral infections. Immune neutralization prevents attachment of viruses to host cells and penetration of the cell membrane. The immune neutralization is dependent on the antibody titer and viral load in the plasma pool. For this reason, Octapharma has introduced the following additional safety measures for octaplasLG® in order to improve the safety margin towards HAV, HEV and parvovirus B19. All batches are tested and released based on the following (in-process or final container) specifications using validated test methods: for anti-HAV IgG ≥1 IU/mL, HAV NAT negative, anti-HEV IgG ≥0.2 IU/mL, anti-B19 IgG ≥11 IU/mL, parvovirus B19 NAT ≤10.0 IU/µL. For these reasons, octaplasLG® is not considered to pose an undue risk of transmitting HAV, HEV or parvovirus B19 to recipients of this product.

In an attempt to further optimize the manufacturing process of Octapharma's S/D treated plasmas, the S/D treatment was reduced from 4–4.5 hours to 1–1.5 hours (by maintaining the other conditions). Validation studies have demonstrated that the S/D method inactivates transfusion relevant viruses within a few minutes to values below the detection limit; therefore, the virus safety profiles of the products were fully maintained. The virus validation studies have been repeated, both under standard and hypothetical robustness conditions. The inactivation kinetics was very fast for HIV-1, Pseudorabies virus (model for HBV) and Sindbis virus (model for HCV and WNV). The reduced S/D treatment time allowed raising the level of plasmin inhibitior from 0.3 to 0.6 IU/mL.[50]

In the prospective clinical studies, only 1 case of a parvovirus B19 seroconversion was observed in a patient, however without any accompanying clinical symptoms. This case was observed before Octapharma introduced additional safety measures into the manufacturing of octaplasLG®, i.e. NAT screening and parvovirus B19 antibody determination.

During the post-marketing phase of octaplas®/octaplasLG®, no transmission of an infectious agent was observed. The virus safety of the product was also confirmed by retrospective surveys.[46,51]

In summary, it can be concluded that octaplasLG® is a safe product regarding the transmission of relevant viruses. There is sufficient information available to assess the viral safety of the product. Bearing in mind the amount of essentially similar drugs already administered to patients without any evidence of virus transmission, further clinical studies in this respect are not justified.

Safety Regarding Variant Creutzfeldt-Jakob Disease (vCJD)

At present, the vCJD agent cannot be routinely detected in blood. However, the hypothesis of the B-lymphocytes and follicular dendritic cells, in particular, acting as potential blood-borne carriers of the vCJD causative agent and its role in neuroinvasion, suggests that leukocyte depletion during processing of blood-derived products will reduce the possibility of transmitting vCJD. For this reason, leukocyte depletion of cellular blood components has been adopted by many countries as a measure to reduce the hypothetical risk of vCJD transmission. octaplas®/octaplasLG® undergoes multiple size exclusion filtration steps, resulting in a complete leukocyte removal without activating the leukocytes.

In addition, Octapharma does not source its plasma from high-risk countries such as the UK for the manufacturing of octaplas®/octaplasLG®, and no animal material is used during the production of this product. Furthermore, it has been suggested that pooling of plasma may decrease infectivity of vCJD below the infectious threshold level due to 1000 times dilution, and finally the octaplas® manufacturing process has also been validated for its ability to reduce prion proteins. The evaluation of the octaplas® manufacturing process to remove potentially present pathologic prion proteins (PrP^{Sc}) revealed an overall capacity of 2.5 $\log_{10}$.[1] A further extension of this removal capacity has been evaluated and a new chromatographic step for the selective binding of PrP^{Sc} to an affinity ligand, developed and optimized for PrP^{Sc} capture (≥9.06 $\log_{10}$ ID/3.8 liters production gel, respectively ≥5.64 $\log_{10}$ ID_{50}/mL gel) and being attached to synthetic resin particles, was implemented into the manufacturing process of octaplasLG®.[1]

7.0 SUMMARY OF RISK VERSUS BENEFIT

Indications claimed for octaplasLG® are similar to those for FFP.

Efficacy data obtained from the clinical trials conducted with octaplas® provide sufficient evidence to conclude that octaplas® and its successor is as effective as standard FFP. In terms of efficacy, standardization represents a clinical benefit in favor of octaplasLG® compared with standard FFP. The virus inactivation/removal and the prion safety measures included in the octaplasLG® manufacturing process represent a substantial therapeutic benefit for patients in terms of safety compared to standard FFP.

The safety profile of octaplasLG® is satisfying and already well described because an impressive amount of post-marketing safety data exists for the product. Only a small number of serious treatment–related AEs were observed in the prospective clinical studies.

Based on all the biochemical features of octaplasLG®, the risk for treatment–related AEs has in reality been reduced to only a limited amount of transfusion-related reactions. In addition, through the pooling of multiple units of FFP, octaplasLG® has been a factor in solving a major problem in transfusion medicine, by eliminating the TRALI problem, especially the immediate death caused by TRALI.

The numerous in vitro characterizations performed with octaplasLG® have caused discussions about the transfusion complications which could potentially result from the reduced levels of protein S and plasmin inhibitor in the product.[37,38,52-55] octaplasLG® should not be used to treat severe deficiencies of these two proteins. Precautionary measures (as mentioned in the proposed package insert) must be taken when octaplasLG® is used in patients at risk for thrombotic complications [48,55-58] and enhanced fibrinolysis [39-41,46]. It is important to note that these patients often underwent long-term, exhausting medical interventions that in itself may have altered the hemostatic

balance.[59] It is also important to note that both thrombosis [60] and hyperfibrinolysis [61-63] are multi-factorial complications.

The virus inactivation/removal included in the octaplasLG® manufacturing process represents a substantial therapeutic benefit for patients in terms of viral safety compared to standard FFP. For octaplasLG®, a new prion affinity column was introduced in the manufacturing process of the product to eliminate potential prion proteins. Additionally, a prion reduction step by ligand chromatography has been implemented in the manufacturing process of octaplasLG®.

When medicinal products prepared from human blood or plasma are given to a patient, the transmission of infectious agents cannot be totally excluded. This applies also to hitherto unknown pathogens. The 3 major requirements to prevent virus transmissions are all met by octaplasLG®, i.e. rigid plasma center selection and donor screening; introduction of appropriate and highly effective manufacturing steps to inactivate/remove viruses; and the testing of the product at appropriate stages for the absence of detectable viruses or markers thereof. The main virus inactivation procedure which is incorporated into the manufacturing process of octaplasLG® is the highly effective S/D treatment, but also immune neutralization contributes to the viral safety of the product. Although no cases of vCJD transmission by blood plasma have been documented, the introduction of a new manufacturing step for the selective binding of the prion proteins is considered to further improve the safety of the octaplasLG® with regards to prion infectivity.

In Europe, at least two countries have converted to completely pathogen-reduced, pooled octaplas® with others following and introducing pathogen-reduction technologies in their plasma manufacturing process.[64]

Specifically the above mentioned safety advantages of octaplasLG® compared to FFP have been clearly recognized in the US filling an unmet medical need by reintroduction of a S/D trated plasma.[65]

After the evaluation of all the available efficacy and safety data and bearing in mind other available therapies, it can be concluded that octaplas®/octaplasLG® offers a positive risk/benefit ratio in the indications intended for clinical use.

8.0 LIST OF ABBREVIATIONS

AEs	Adverse Event(s)
aPTT/APTT	Activated Partial Thromboplastin Time
BLA	Biological License Application
BW	Body Weight
CSP	Cryosupernatant
DIC	Disseminated Intravascular Coagulation
FFP	Fresh-Frozen Plasma
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C virus
HEV	Hepatitis E virus
HGV	Hepatitis G virus
HIV	Human Immunodeficiency Virus
HLA	Human Lymphocyte Antigen
INR	International Normalization Ratio
IU	International Unit
LD	Liver Disease
LTX	Liver Transplantation
NAT	Nucleic Acid Amplification Testing
PCC	Prothrombin complex concentrates
PEX	Plasma Exchange
PT	Prothrombin time
PrP^{Sc}	Prion Proteins
S/D	Solvent/Detergent
TNBP	Tri(n-butyl)phosphate
TRALI	Transfusion Related Acute Lung Injury
TTP	Thrombotic Thrombocytopenic Purpura
VACV	Vaccinia Virus
vCJD	Variant Creutzfeldt-Jakob Disease
VTE	Venous Thromboembolism
WNV	West Nile Virus

9.0 LIST OF TABLES

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Reference List

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